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Vitamin D receptor *FokI*, *BsmI*, and *TaqI* polymorphisms and susceptibility to rheumatoid arthritis

A meta-analysis

Rheumatoid arthritis (RA) is a chronic inflammatory disease predominantly affecting the synovial joints and suffered by up to 1% of adults worldwide. Human leukocyte antigen (HLA) class II molecules have been shown to be strongly associated with RA, but family studies suggest that this association accounts for only one third of genetic susceptibility and that non-HLA genes are also involved [1, 2].

Although the primary function of vitamin D is regulation of bone mineral homeostasis, it is also involved in interleukin (IL)-2 inhibition, antibody production, and lymphocyte proliferation; therefore, vitamin D is considered to be a regulator of the immune system [3]. It is known that 1,25-dihydroxy vitamin D₃ (1,25(OH)₂D₃) inhibits interferon secretion and negatively regulates IL-12 production by downregulating nuclear factor-kappa B [4]. Furthermore, in one in vitro study, 1,25(OH)₂D₃ was found to have a preventative effect on autoimmune diseases [5].

The action of vitamin D is dependent on the vitamin D receptor (VDR), a member of the nuclear hormone receptor superfamily, and the *VDR* gene is one of the most frequently studied genes in the context of RA. This gene is located on chromosome 12q13.11 [6], and three polymorphisms—*BsmI* (rs1544410) and *Apal* (rs7975232), both in intron 8; and *TaqI* (rs731236) in exon 9—have been identified at the 3'-end of the gene and been shown to be in strong linkage disequilibrium (LD; [7]).

The other polymorphic region, *FokI* (rs10735810), is located in the start codon [6]. Although the functional significances of these four *VDR* polymorphisms remains unknown, it is believed that LD and one or more functional polymorphism(s) elsewhere in the *VDR* gene explain the observed associations between *VDR* gene polymorphisms and autoimmune diseases. These *VDR* polymorphisms have been associated with RA in some reports, but by no means in all [8, 9, 10, 11, 12]. The reasons for this disparity may be small sample sizes, low statistical power, and/or clinical heterogeneity [13, 14, 15]. Therefore, in order to overcome the limitations of individual studies, resolve inconsistencies, and reduce the likelihood that random errors are responsible for false-positive or false-negative associations, we turned to meta-analysis. The aim of the present study was to determine using meta-analysis whether the *VDR FokI*, *BsmI*, and *TaqI* polymorphisms are associated with susceptibility to RA.

Methods

Identification of eligible studies and data extraction

Literature search

We performed a search for studies that examined associations between *VDR* polymorphisms and RA. The literature was searched using the MEDLINE, EMBASE, and Cochrane citation databases to identify

available articles in which *VDR* polymorphisms were analyzed in RA patients. Combinations of keywords, such as, 'vitamin D,' 'VDR,' 'polymorphism,' 'rheumatoid arthritis,' and 'RA' were entered as Medical Subject Headings (MeSH) or text words. References in identified studies were also investigated to identify additional studies not indexed by the electronic databases. No language or country restrictions were applied.

Inclusion criteria

Studies were included if: (1) they were case-control studies; (2) the data were original (independence among studies); (3) they provided enough data to calculate an odds ratio (OR); (4) they had a distribution of the *VDR* polymorphism in normal controls consistent with the Hardy-Weinberg equilibrium (HWE).

Exclusion criteria

The following studies were excluded: (1) studies that contained overlapping data; (2) studies in which the number of null and wild type genotypes could not be ascertained; and (3) studies in which family members were studied, because these analyses are based on linkage considerations.

Data extraction

We conducted a systematic review and meta-analysis in accordance with the guidelines provided by the Preferred Reporting Items for Systematic Reviews and

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Tab. 1 Characteristics of individual studies included in the meta-analysis

| Study [Ref] | Country | Ethnicity | Numbers | | Polymorphism(s) | Association of findings | Quality score |
|--------------------------------|----------------|-----------|---------|---------|-------------------------|--|---------------|
| | | | Case | Control | | | |
| Karray et al. 2012 [8] | Tunisia | Tunisian | 108 | 152 | <i>FokI, BsmI</i> | <i>FokI</i> (p=0.001), <i>BsmI</i> (NS) | 6 |
| Chelani-1 et al. 2011 [12] | United Kingdom | Asian | 130 | 146 | <i>FokI, BsmI</i> | <i>FokI</i> (NS), <i>BsmI</i> (p<0.001) | 5 |
| Chelani-2 et al. 2011 [12] | United Kingdom | European | 132 | 144 | <i>FokI, BsmI</i> | NS | 5 |
| Maalej-1 et al. 2005 [9] | France | European | 100 | 100 | <i>FokI, BsmI, TaqI</i> | <i>FokI</i> (p=0.01), <i>BsmI</i> (NS), <i>TaqI</i> (NS) | 6 |
| Maalej-2 et al. 2005 [9] | France | European | 271 | 130 | <i>FokI</i> | NS | 5 |
| Goertz et al. 2003 [10] | Germany | European | 62 | 40 | <i>FokI, BsmI, TaqI</i> | <i>FokI</i> (NS), <i>BsmI</i> (p=0.026), <i>TaqI</i> (p=0.017) | 4 |
| Garcia-Lozano et al. 2001 [11] | Spain | European | 120 | 200 | <i>BsmI, TaqI</i> | NS | 5 |

Ref reference, *NS* not significant.

Tab. 2 Meta-analysis of the associations between the vitamin D receptor (*VDR*) *FokI* and *BsmI* polymorphisms and rheumatoid arthritis

| Polymorphism | Population | No. of studies | Test of association | | | Test of heterogeneity ^a | | | Publication bias p-value |
|----------------------------|------------|----------------|---------------------|-------------|---------|------------------------------------|---------|----------------|--------------------------|
| | | | OR | 95% CI | p-value | Model | p-value | I ² | |
| <i>FokI</i> | | | | | | | | | |
| F vs. f | Overall | 6 | 1.174 | 0.994–1.387 | 0.059 | F | 0.170 | 35.5 | 0.192 |
| | European | 4 | 1.402 | 1.126–1.746 | 0.003 | F | 0.629 | 0 | |
| FF vs. Ff + ff (recessive) | Overall | 6 | 1.249 | 0.997–1.564 | 0.054 | F | 0.100 | 45.8 | 0.098 |
| | European | 4 | 1.611 | 1.203–2.158 | 0.001 | F | 0.620 | 0 | |
| FF + Ff vs. ff (dominant) | Overall | 6 | 1.164 | 0.827–1.637 | 0.384 | F | 0.738 | 0 | 0.761 |
| | European | 4 | 1.322 | 0.834–2.095 | 0.234 | F | 0.553 | 0 | |
| FF vs. ff | Overall | 6 | 1.261 | 0.875–1.817 | 0.214 | F | 0.414 | 0.25 | 0.675 |
| | European | 4 | 1.652 | 1.013–2.693 | 0.044 | F | 0.510 | 0 | |
| <i>BsmI</i> | | | | | | | | | |
| B vs. b | Overall | 6 | 1.065 | 0.911–1.245 | 0.427 | F | 0.000 | 94.8 | 0.265 |
| | European | 4 | 1.057 | 0.866–1.291 | 0.583 | F | 0.000 | 96.8 | |
| BB vs. Bb + bb (recessive) | Overall | 6 | 1.169 | 0.909–1.504 | 0.224 | F | 0.016 | 63.9 | 0.268 |
| | European | 4 | 1.474 | 1.067–2.036 | 0.019 | F | 0.031 | 66.1 | |
| BB + Bb vs. bb (dominant) | Overall | 6 | 0.826 | 0.654–1.042 | 0.106 | F | 0.501 | 0 | 0.133 |
| | European | 4 | 0.788 | 0.597–1.058 | 0.113 | F | 0.253 | 26.4 | |
| BB vs. bb | Overall | 6 | 0.957 | 0.711–1.289 | 0.772 | F | 0.933 | 0 | 0.970 |
| | European | 4 | 1.084 | 0.739–1.592 | 0.679 | F | 0.961 | 0 | |

^aI²=0 indicates absence of heterogeneity *VDR* vitamin D receptor, *OR* odds ratio, *CI* confidence interval, *F* Fixed effects model.

Tab. 3 Meta-analysis of the association between the vitamin D receptor (*VDR*) *TaqI* polymorphism and rheumatoid arthritis

| Polymorphism | Population | No. of studies | Test of association | | | Test of heterogeneity ^a | | | Publication bias p-value |
|----------------------------|------------|----------------|---------------------|-------------|---------|------------------------------------|---------|----------------|--------------------------|
| | | | OR | 95% CI | p-value | Model | p-value | I ² | |
| <i>TaqI</i> | | | | | | | | | |
| T vs. t | Overall | 3 | 1.065 | 0.834–1.361 | 0.613 | F | 0.211 | 35.7 | 0.076 |
| | European | 3 | 1.065 | 0.834–1.361 | 0.613 | F | 0.211 | 35.7 | |
| TT vs. Tt + tt (recessive) | Overall | 3 | 1.243 | 0.891–1.735 | 0.200 | F | 0.147 | 47.8 | 0.324 |
| | European | 3 | 1.243 | 0.891–1.735 | 0.200 | F | 0.147 | 47.8 | |
| TT + Tt vs. tt (dominant) | Overall | 3 | 0.823 | 0.500–1.354 | 0.443 | F | 0.491 | 0 | 0.353 |
| | European | 3 | 1.243 | 0.891–1.735 | 0.200 | F | 0.147 | 47.8 | |
| TT vs. tt | Overall | 3 | 1.022 | 0.599–1.742 | 0.937 | F | 0.422 | 0 | 0.138 |
| | European | 3 | 1.243 | 0.891–1.735 | 0.200 | F | 0.147 | 47.8 | |

^aI²=0 indicates absence of heterogeneity *VDR* vitamin D receptor, *OR* odds ratio, *CI* confidence interval, *F* Fixed effects model.

Meta-Analyses (PRISMA) statement. Regarding the methods and results of meta-analysis, data were extracted from original studies by two independent reviewers. Discrepancy between the reviewers was resolved by consensus or a third reviewer. The following information was extracted from each study: author, year of publication, ethnicity of the study population, demographics, and numbers of cases and controls for the *FokI*, *BsmI*, and *TaqI* genotypes. Frequencies of alleles were calculated from corresponding genotype distributions.

Evaluations of statistical associations

We performed meta-analyses using: (1) allelic contrast, (2) contrast of homozygotes, (3) recessive, and (4) dominant models. Point estimates of risk, ORs, and 95% confidence intervals (CI) were estimated for each study. In addition, intra- and interstudy variations or heterogeneities were assessed using Cochran's Q-statistic. This heterogeneity test assesses the null hypothesis that all studies evaluated the same effect. The effect of heterogeneity was quantified using I^2 , which ranges between 0 and 100% and represents the proportion of interstudy variability that can be attributed to heterogeneity as opposed to chance [16]. I^2 values of 25, 50, and 75% were nominally assigned as low, moderate, and high estimates, respectively. The fixed effects model assumes that genetic factors have similar effects on RA susceptibility across all investigated studies, and that observed variations among studies are caused by chance alone [17]. The random effects model assumes that different studies show substantial diversity and assesses both intrastudy sampling error and interstudy variance [18]. We used the fixed effects model in this meta-analysis. Statistical manipulations were undertaken using the Comprehensive Meta-Analysis computer program (Biosoft, Englewood, NJ, USA).

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Vitamin D receptor *FokI*, *BsmI*, and *TaqI* polymorphisms and susceptibility to rheumatoid arthritis. A meta-analysis

Abstract

Objective. The aim of this study was to explore whether vitamin D receptor (*VDR*) polymorphisms are associated with susceptibility to rheumatoid arthritis (RA).

Methods. Meta-analyses were conducted on the associations between the *VDR FokI*, *BsmI*, and *TaqI* polymorphisms and RA.

Results. A total of seven studies were considered in the meta-analysis, involving a total of 923 patients and 912 controls. Meta-analysis of the *VDR FokI* polymorphism showed no association between RA and the F allele in the entire studied cohort (odds ratio, OR = 1.1740, 95% confidence interval, CI = 0.994–1.387, $p=0.059$). However, stratification by ethnicity revealed a significant association between the F allele and RA in Europeans (OR = 1.402, 95% CI = 1.126–1.746,

$p=0.003$). Furthermore, an association was found between RA and the *VDR FokI* polymorphism using both the dominant model and homozygote contrast. Meta-analysis revealed no association between RA and the *VDR BsmI* B and *TaqI* T polymorphisms in Europeans (OR for the B allele = 1.065, 95% CI = 0.911–1.245, $p=0.427$; OR for the T allele = 1.065, 95% CI = 0.834–1.361, $p=0.613$). **Conclusion.** This meta-analysis suggests that the *VDR FokI* polymorphism is associated with susceptibility to RA in European populations.

Keywords

Immune system · Autoimmune diseases · Hormone receptors, nuclear · MEDLINE · Linkage disequilibrium

FokI, *BsmI* und *TaqI*-Polymorphismus des Vitamin-D-Rezeptors und Anfälligkeit für rheumatoide Arthritis. Eine Metaanalyse

Zusammenfassung

Ziel. Ziel der vorliegenden Studie war es zu untersuchen, ob Vitamin-D-Rezeptor (*VDR*)-Polymorphismen mit der Anfälligkeit für rheumatoide Arthritis (RA) in Zusammenhang stehen.

Methoden. Es wurden Metaanalysen zu den Assoziationen zwischen den *FokI*-, *BsmI*- und *TaqI*-Polymorphismen des *VDR* und RA durchgeführt.

Ergebnisse. In der Metaanalyse wurden 7 Studien berücksichtigt, die 923 Patienten und 912 Kontrollen umfassten. Die Metaanalyse des *VDR-FokI*-Polymorphismus ergab keine Assoziation zwischen RA und dem F-Allel in der gesamten untersuchten Kohorte (Odds Ratio, OR = 1,1740; 95%-Konfidenzintervall, 95%-KI = 0,994–1,387; $p=0,059$). Jedoch zeigte die Stratifizierung nach Ethnizität eine signifikante Assoziation zwischen dem F-Allel und RA bei Europäern (OR = 1,402; 95%-KI = 1,126–1,746; $p=0,003$). Darüber hinaus

wurde eine Assoziation zwischen RA und dem *VDR-FokI*-Polymorphismus anhand des dominanten Modells und des homozygoten Kontrasts festgestellt. Wie die Metaanalyse zeigte, bestand keine Assoziation zwischen RA und den *VDR-BsmI*-B- und *TaqI*-T-Polymorphismen bei Europäern (OR für das B-Allel = 1,065; 95%-KI = 0,911–1,245; $p=0,427$; OR für das T-Allel = 1,065; 95%-KI = 0,834–1,361; $p=0,613$).

Schlussfolgerung. Die vorliegende Metaanalyse liefert Hinweise darauf, dass der *VDR-FokI*-Polymorphismus mit der Anfälligkeit für RA in der europäischen Bevölkerung assoziiert ist.

Schlüsselwörter

Immunsystem · Autoimmunkrankheit · Hormonrezeptoren, nukleäre · MEDLINE · Kopplungsungleichgewicht

Evaluation of quality score assessment, sensitivity test, and publication bias

The included studies were scored by the two reviewers, based on criteria selected from published recommendations on the evaluation of the quality of genetic association studies [19]; any disagreement was

adjudicated by a third author. Total scores ranged from 0 to 10. Sensitivity analysis was also performed; firstly to assess the influence of each study on the pooled OR (by omitting each individual study) and secondly, to evaluate the statistical robustness of the results. Funnel plots are often used to detect publication bias. However, due to the limitations of funnel plotting,

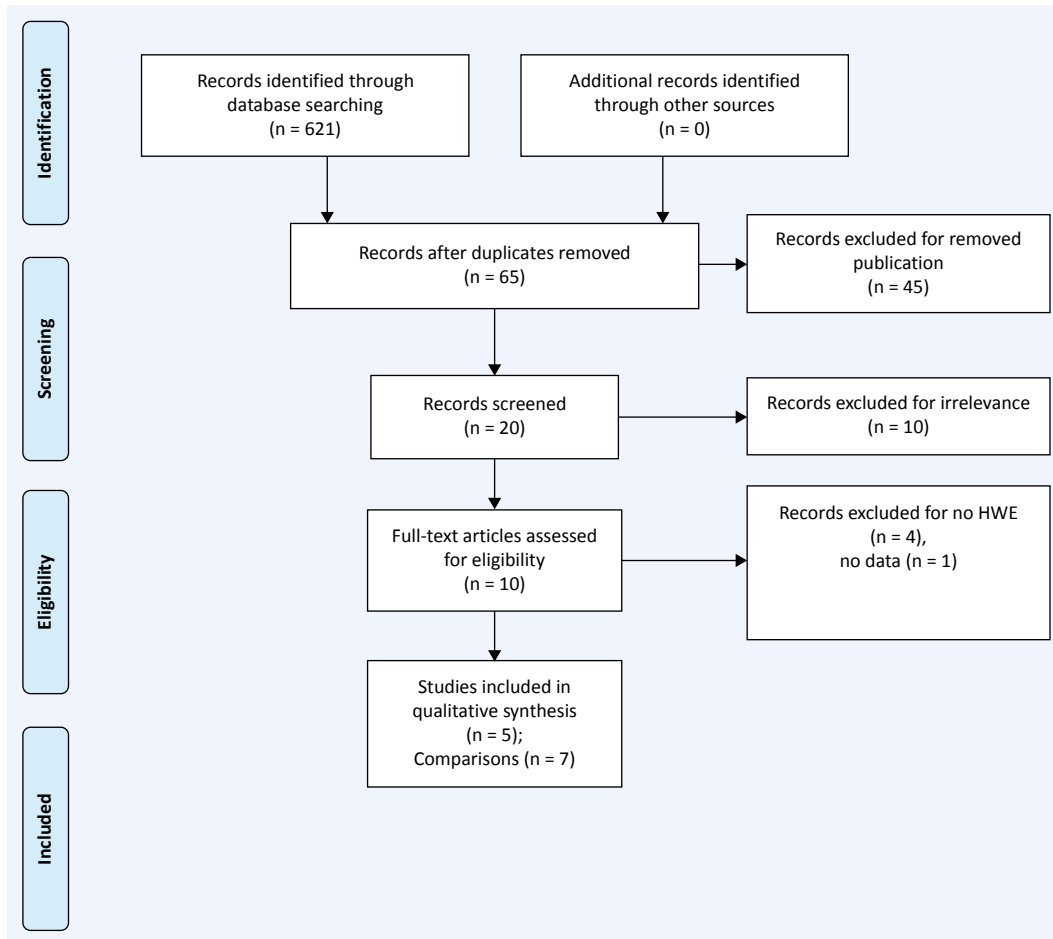


Fig. 1 ◀ Study flow chart

which requires a range of studies of varying sizes involving subjective judgments, publication bias was evaluated using Egger's linear regression test [20], which measures funnel plot asymmetry using a natural logarithm scale of OR.

Results

Studies included in the meta-analysis

In total, 621 studies were identified by electronic and manual searches, and 10 were selected for a full-text review based on title and abstract details [8, 9, 10, 11, 12, 21, 22, 23, 24, 25]. Five of these 10 studies were excluded; four because they had a genotype distribution in controls that was inconsistent with the HWE [21, 22, 23, 24] and one because it did not include the *FokI*, *BsmI*, and *TaqI* polymorphisms [25]. Five studies thus met the inclusion criteria [8, 9, 10, 11, 12]. Two of the eligible studies contained data on two different groups

[9, 12] and these groups were treated independently. The study selection protocol is illustrated in Fig. 1. Therefore, a total of seven separate comparisons were considered in the meta-analysis, comprising 923 patients and 912 controls in total (Tab. 1). These seven studies included one Asian, one Tunisian, and five European populations. An ethnicity-specific meta-analysis was thus conducted for European populations. Six studies examined the *VDR FokI* polymorphism, six the *VDR BsmI* polymorphism, and three the *VDR TaqI* polymorphism. Selected characteristics of these studies with respect to associations between the *VDR* polymorphisms and RA are summarized in Tab. 1.

Meta-analysis of relationships between *VDR* polymorphisms and rheumatoid arthritis

A summary of the meta-analysis findings regarding the association between the

different *VDR* polymorphisms and RA is provided in Tab. 2 and Tab. 3.

FokI polymorphism

Meta-analysis of the *VDR FokI* polymorphism showed no association between RA and the F allele in all study subjects (OR =1.1740, 95% CI =0.994–1.387, $p=0.059$; Tab. 2, Fig. 2). However, stratification by ethnicity revealed a significant association between the F allele and RA in Europeans (OR =1.402, 95% CI =1.126–1.746, $p=0.003$; Tab. 2, Fig. 3). Furthermore, an association was found between RA and the *VDR FokI* polymorphism using both the dominant model and the homozygote contrast (Tab. 2).

BsmI polymorphism

Meta-analysis revealed no association between RA and the *BsmI* B allele in all study subjects (OR =1.065, 95% CI =0.911–1.245, $p=0.427$; Tab. 2, Fig. 2). Stratification by ethnicity indicated an associa-

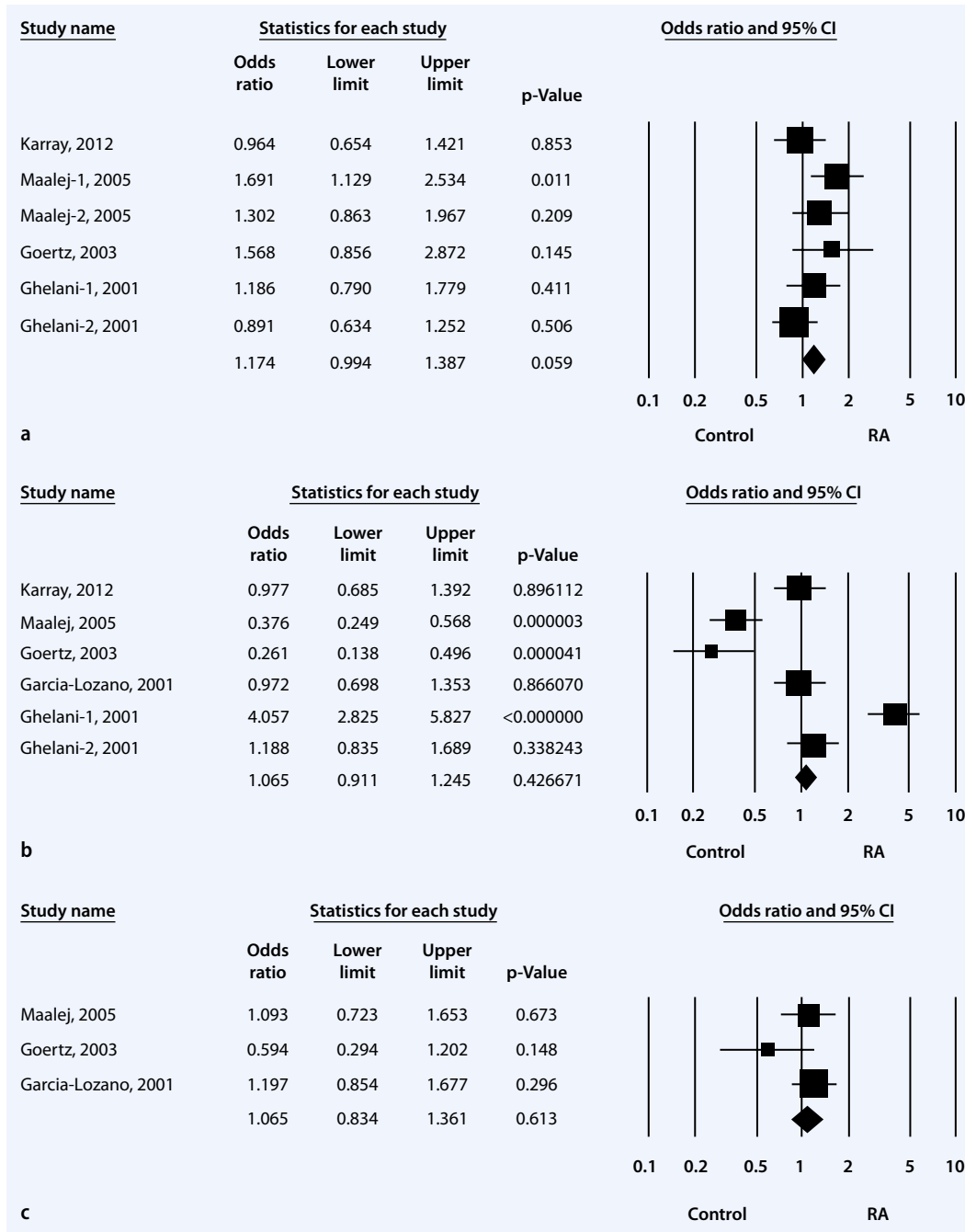


Fig. 2 ◀ Odds ratios and 95% confidence intervals (CI) of individual studies and pooled data for the allelic associations between the vitamin D receptor (VDR) *FokI* (a), *BsmI* (b), and *TaqI* (c) polymorphisms and rheumatoid arthritis (RA)

tion between the VDR *BsmI* allele and RA in Europeans (OR =1.474, 95% CI =1.067–2.036, $p=0.019$; ■ **Tab. 2**). However, there was a high heterogeneity in the meta-analysis and the random effects model showed no association (OR =0.801, 95% CI =0.251–2.562, $p=0.709$). The recessive and dominant models, as well as homozygote contrast failed to reveal an association between the *BsmI* polymorphism and RA in all subjects (■ **Tab. 2**).

TaqI polymorphism

Meta-analysis indicated no association between RA and the *TaqI* T allele in the European populations (OR =1.065, 95% CI =0.834–1.361, $p=0.613$; ■ **Tab. 3**; ■ **Fig. 2**). The recessive and dominant models, as well as homozygote contrast failed to reveal an association between the *TaqI* polymorphism and RA (■ **Tab. 3**).

Heterogeneity, sensitivity test, and publication bias

Some interstudy heterogeneity was found during the meta-analysis of the VDR *BsmI* polymorphism. However, no interstudy heterogeneity was found during the meta-analyses of the VDR *FokI* and *TaqI* polymorphisms.

Sensitivity analysis was performed to assess the influence of each individual study on the pooled OR by removing each

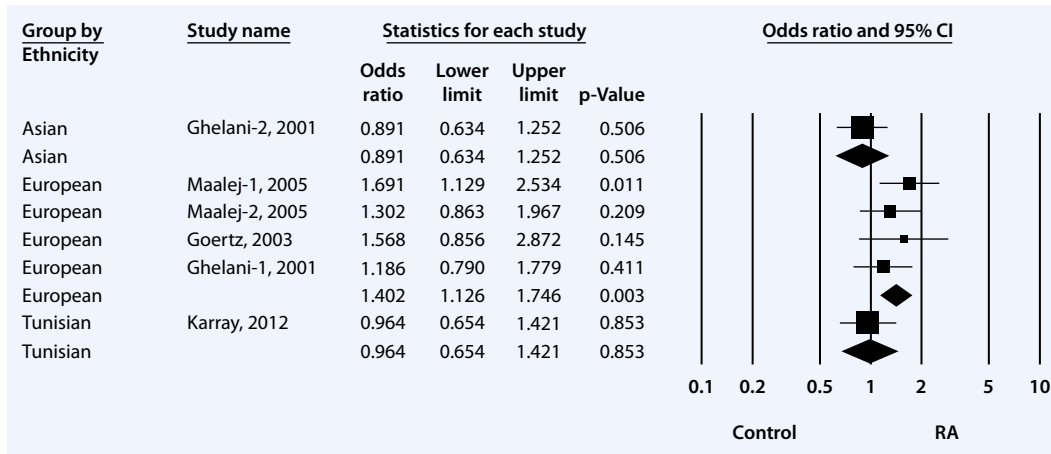


Fig. 3 ◀ Odds ratios and 95% confidence intervals (CI) of individual studies and pooled data for the associations between the F allele of the vitamin D receptor (VDR) *FokI* polymorphism and rheumatoid arthritis (RA) in each ethnic group

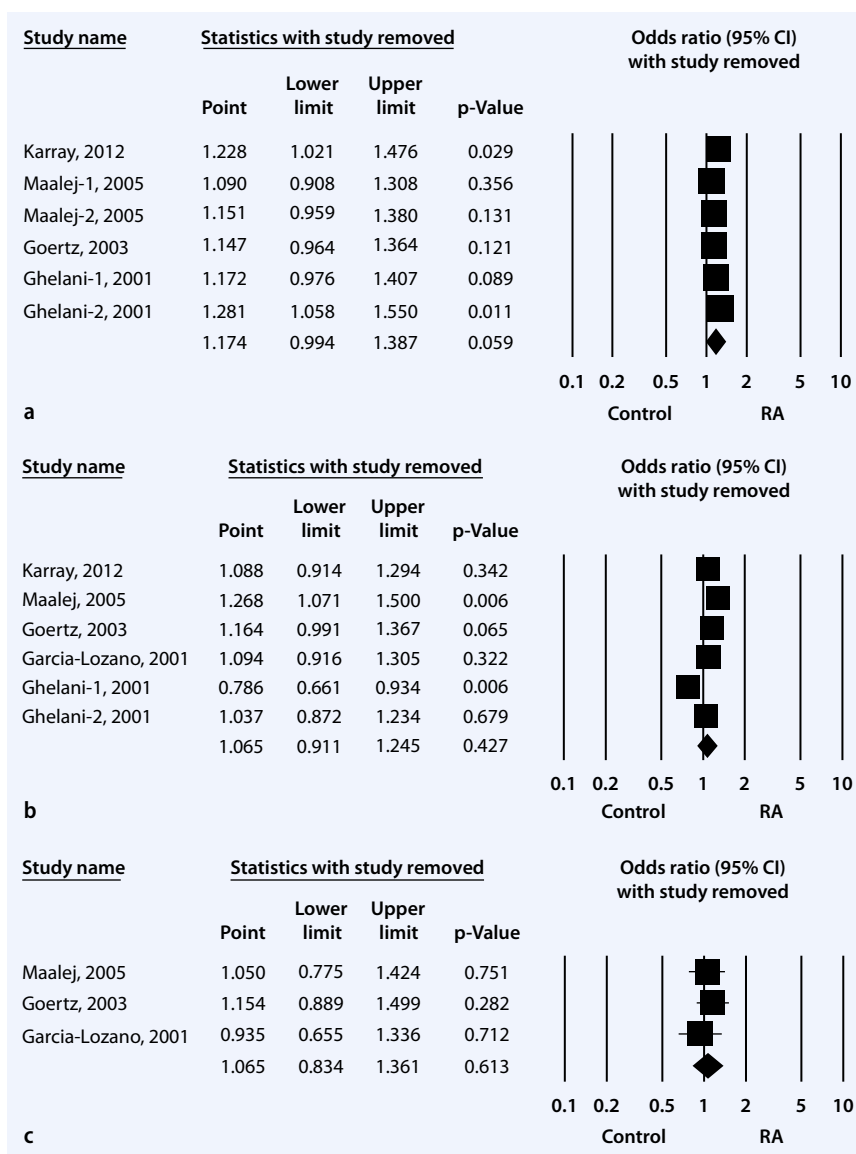


Fig. 4 ▲ Sensitivity analysis of studies examining the allelic associations between the vitamin D receptor (VDR) *FokI* (a), *BsmI* (b), and *TaqI* (c) polymorphisms and rheumatoid arthritis (RA) in all subjects

study in turn and recalculating the pooled OR. This analysis showed that no individual study significantly affected the pooled OR of the VDR *TaqI* polymorphism, indicating statistically robust results from this meta-analysis. After the study of Karray et al. or Ghelani-2 et al. was excluded, the results of the VDR *FokI* polymorphism were changed (OR =1.228, 95% CI =1.021–1.476, $p=0.029$; OR =1.281, 95% CI =1.058–1.550, $p=0.011$; ■ Fig. 4). When the study of Maalej et al. or Ghelani-1 et al. was excluded, the results of the VDR *BsmI* polymorphism changed (OR =1.268, 95% CI =1.071–1.500, $p=0.006$; OR =0.786, 95% CI =0.661–0.934, $p=0.006$; ■ Fig. 4). However, when two studies [9, 10] at one side of the vertical line and one study [12] at the opposite side were excluded, the results of the VDR *BsmI* polymorphism did not change and heterogeneity disappeared (OR =1.038, 95% CI =0.850–1.267, $p=0.714$; $I^2=0$, heterogeneity $p=0.661$).

It was difficult to correlate the funnel plot, which is usually used to detect publication bias, as the number of studies included in the analysis was relatively small. However, Egger's regression test showed no evidence of publication bias (■ Tab. 2, 3, ■ Fig. 5).

Discussion

Although the multifactorial natures of autoimmune diseases are well recognized, genetic factors are considered to be strong determinants of these diseases, and researchers have thus been encouraged to search for the genes responsible. Many genes have been studied in this context; the VDR gene being an example of

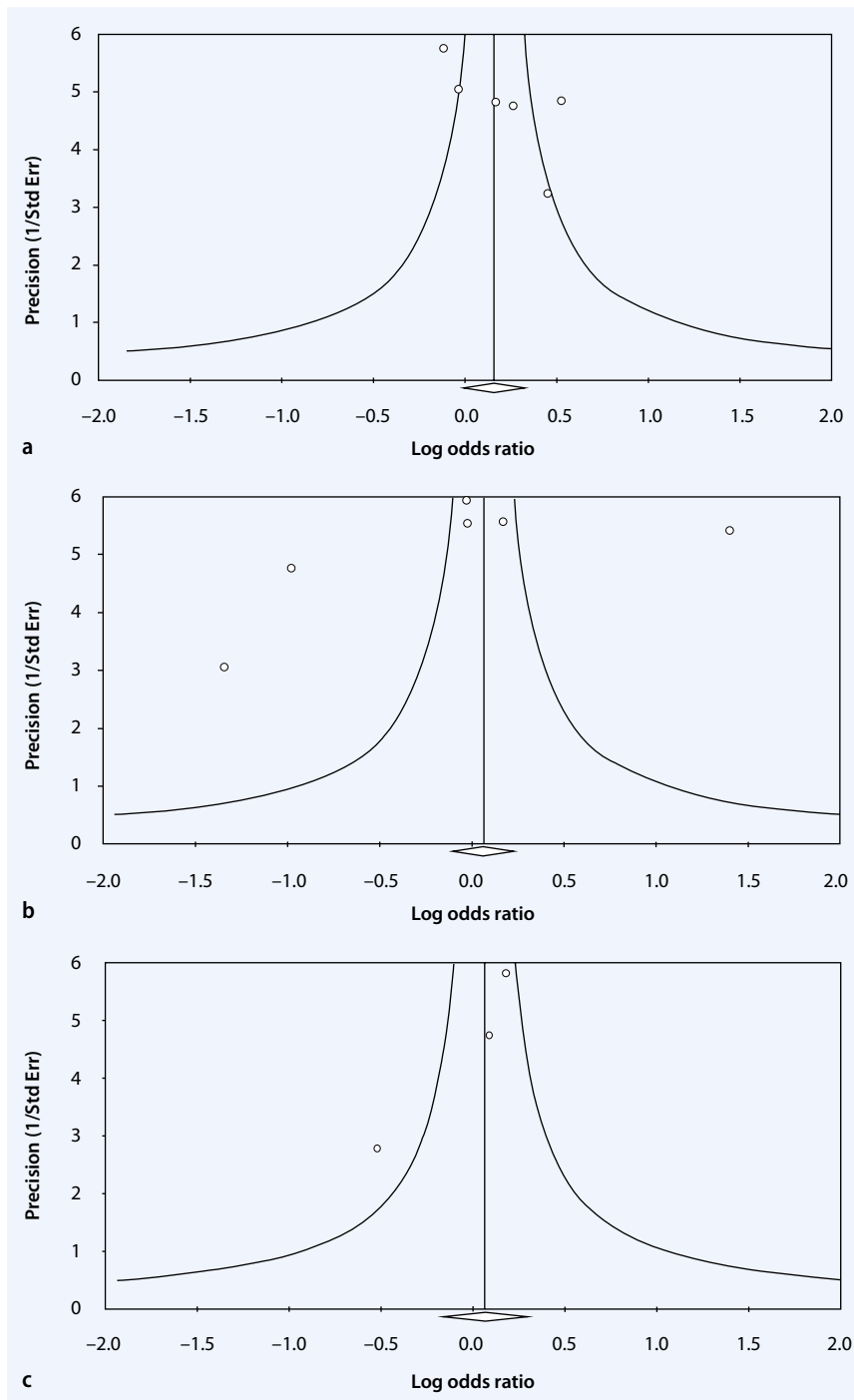


Fig. 5 ▲ Funnel plots of studies examining the allelic associations between the vitamin D receptor (VDR) *FokI* (a), *BsmI* (b), and *TaqI* (c) polymorphisms and rheumatoid arthritis (RA) in all subjects. SE standard error (Egger's regression p-values = 0.192, 0.265, 0.076, for a, b, and c, respectively)

those studied in the context of RA [26]. Vitamin D plays a key role in calcium homeostasis and also contributes to regulation of the immune system [3]. Given the immunosuppressive effects of vitamin D and the potential link between vitamin D deficiency and autoimmune diseases, VDR polymorphisms, which may influ-

ence VDR activity, have been studied as potential causes of autoimmune diseases, including RA [27, 28].

In this meta-analysis, we combined data from published studies to evaluate genetic associations between the most commonly studied polymorphisms of the VDR gene, namely the *FokI*, *BsmI*, and

TaqI polymorphisms, and RA. Our meta-analysis of the VDR *BsmI* and *TaqI* polymorphisms showed no association with RA; neither in all study subjects nor in Europeans. In contrast, meta-analysis of the *FokI* polymorphism showed a significant association with RA in European populations (OR = 1.402, 95% CI = 1.126–1.746, $p=0.003$) without heterogeneity, suggesting that the VDR *FokI* F allele may be a risk factor for RA in Europeans.

However, our results should be interpreted with caution because of the limited number of studies included in this meta-analysis, which also restricted further subgroup analyses. High heterogeneity was observed in the VDR polymorphism meta-analysis, and sensitivity analysis performed by removing each study in turn, revealed that the results of meta-analysis of the VDR *FokI* and *BsmI* polymorphisms were not statistically robust. Furthermore, the relative importance of the VDR polymorphisms during the development of RA may be dependent on ethnicity. We were able to perform ethnicity-specific meta-analysis of the *FokI* polymorphism only in the European patients.

The *FokI* and *BsmI* polymorphisms have a functional role. The *FokI* polymorphism located in a start codon creates an alternative start site, resulting in a protein of different length [29]. The short protein (F allele) is more active than the long variant (f allele) with respect to its transactivation activity [30]. Vitamin D concentration was significantly increased in patients with the ff genotype compared to individuals carrying the FF genotype [30]. VDR mRNA level was significantly decreased in patients with the VDR B allele compared to those not having the B allele [31]. However, our results are not consistent with these functional studies of the VDR *BsmI* polymorphism. Epidemiologic results often do not coincide with functional studies, because RA is a complex disease; with contributions from multiple genes, different genetic backgrounds, and environmental factors. The VDR *BsmI* polymorphism might not be associated with RA susceptibility, but rather with RA severity or clinical findings. Additionally, our results on the VDR *BsmI* polymorphism might be due to type II error.

The present study has some limitations that require consideration. Firstly, heterogeneity and confounding factors may have distorted the analysis. Secondly, ethnicity-specific analysis included data from European patients; therefore, the results are only applicable to that particular ethnic group. Thirdly, haplotype analysis may have provided more information and would have been more powerful than single polymorphism analysis. Furthermore, LD was found for the *BsmI*, *TaqI*, and *Apal* polymorphisms [7]. However, no meta-analysis of haplotypes was possible due to inadequate haplotype data. Fourthly, the *VDR* polymorphisms may be associated with RA severity and clinical features, but the small amount of available data did not allow us to investigate these associations.

Conclusion

This meta-analysis demonstrates that the *VDR FokI* polymorphism is associated with susceptibility to RA in European populations. However, an association was not found between the *VDR BsmI* and *TaqI* polymorphisms and RA. Larger-scale studies in populations with different ethnicities are necessary to explore the roles of *VDR* gene polymorphisms in the pathogenesis of RA.

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Compliance with ethical guidelines

Conflict of interest. G.G. Song, S.-C. Bae, and Y.H. Lee state that there are no conflicts of interest.

The accompanying manuscript does not include studies on humans or animals.

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